REMARKS

IN THE CLAIMS

Claim 1 has been amended for greater clarity and particularity to point out the subject matter regarded by Applicants as their invention. Applicants respectfully submit that that amendment to Claim 1 suggested by the Examiner has a clear support in the in the instant application, for example, in original Claim 24.

As suggested by the Examiner at page 4 of the instant Office Action, method step (d) of Claim 1 has been amended to recite a method wherein the MN/CA IX expression level indicative of "poorer prognosis" is compared to a second particular type of expression:

> (d) determining that said subject vertebrate has a poorer prognosis if the level of MN/CA IX protein or MN/CA IX polypeptide of step (b) is higher than the average level of MN/CA IX protein or MN/CA IX polypeptide in said comparable samples**, than if said MN/CA IX protein or MN/CA IX polypeptide of step (b) were absent or at a significantly reduced level in said sample relative to said average level**; . . . .

[Emphasis added.] Applicants respectfully submit that one of skill in the art would understand that if a higher than average MN/CA IX expression level indicates "poorer" prognosis, that prognosis is relative to the prognosis indicated by any other MN/CA IX expression level (such as, "absent or at a significantly reduced level in said sample relative to said average level . . ."). Support for the amendment to Claim 1(d) can be found at least in the method step (c) of original Claim 24 which reads:

> (c) concluding that if said MN/CA9 gene expression product is neither absent for at such a significantly reduced level in said invasion front sample, that the subject vertebrate has a poorer prognosis than if said MN/CA9 gene expression product were absent or at a such a significantly reduced level in said invasion front sample.

Applicants respectfully conclude that no new matter has been entered by the above amendment. Applicants also respectfully conclude that the amendment to Claim 1 brings the rejected claims in "condition for allowance" in accordance with MPEP § 714.12, and request entry of said amendment.

I. 35 USC 112, Second Paragraph Rejection

The rejection of Claim 1 under 35 USC 112, second paragraph, has been maintained. The Examiner stated on the bottom of page 4 of the Office Action:

> To obviate the rejection, Applicant may want to amend claim 1 to incorporate language analogous to that of part "c" of claim 24, which recites a method wherein a subject with a first particular type of expression has a poorer prognosis *than if said subject had a second particular type of expression*.

Applicants have followed the Examiner's suggestion, and amended Claim 1's step (d) to incorporate the language of part "c" of Claim 24 which the Examiner indicated. Step (d) of Claim 1 now reads:

> (d) determining that said subject vertebrate has a poorer prognosis if the level of MN/CA IX protein or MN/CA IX polypeptide of step (b) is higher than the average level of MN/CA IX protein or MN/CA IX polypeptide in said comparable samples**, than if said MN/CA IX protein or MN/CA IX polypeptide of step (b) were absent or at a significantly reduced level in said sample relative to said average level**;

[Emphasis added.] Applicants respectfully conclude that amendment to Claim 1 obviates the subject rejection and respectfully request that the Examiner withdraw the instant 35 USC § 112, second paragraph rejection.

II. 35 USC 112, First Paragraph Rejection – Written Description

The rejection of Claims 1-11, 14, 16 and 18-24 under 35 USC 112, first paragraph, as "failing to comply with the written description requirement, is maintained. . . ." [Office Action, at page 5.] The Office Action states at the bottom of page 5:

> The specification does not disclose and the prior art does not teach the genera of tissue samples taken from a subject vertebrate with a disease that affects a tissue which normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis.

Applicants respectfully traverse, relying upon the arguments made in their 08/16/07 response to the first Office Action (dated 05/17/07), which arguments are herein incorporated by reference, and then by addressing any additional points made in the instant Office Action. Applicants respectfully remind the Examiner that numerous cases hold that an "original claim," that is, one contained in the Specification when it is filed complies with the § 112 1st written description requirement. For example, the Court of Customs and Patent Appeals (CCPA)[1] in In re Smith, 481 F.2d 910, 178 USPQ 620 at 623 (CCPA 1973) stated: "Where the claim is an original claim, **the underlying concept of insuring disclosure as of the filing date is satisfied, and the description requirement has likewise been held to be satisfied.**" [Emphasis added.]

> The Manual of Patent Examining Procedure in Section 2163(I)- (II) states:
>
> There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) ("we are of the opinion that the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims").
>
> . . . .
>
> Consequently, rejection of an original claim for lack of written description should be rare.

[Emphasis added.]

The PTO's Written Description Guidelines [Fed. Reg., Vol. 66, No. 4 (Jan. 5, 2001)] similarly indicate that there is a "strong presumption that an adequate written

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1. The CCPA is a predecessor court to the Court of Appeals for the Federal Circuit. In the Federal Circuit's first reported opinion, South Corp. v. United States, 215 USPQ 657 (Fed. Cir. 1982), the Federal Circuit adopted as binding precedent "the holdings of our predecessor courts, the United States Court of Claims and the United States Court of Customs and Patent Appeals [CCPA]. . . ."

description of the claimed invention is present when the application is filed, consistent with In re Wertheim, supra.

> The Guidelines emphasize that the burden of proof is on the **examiner to establish that a description as filed is not adequate and require the examiner to introduce sufficient evidence or technical reasoning to shift the burden of going forward with contrary evidence to the applicant**.

[*Id*. at page 1100, col. 3; emphasis added.] Applicants respectfully submit that the Examiner has not introduced sufficient evidence to shift the initial burden of proof to the Applicants, but if **hypothetically** that burden had been shifted, the Applicants have demonstrated that that burden would be overturned.

Applicants respectfully point out that the Examiner is mistaken as to the prior art being limited to a description of gastric and gallbladder cancer samples, submitting as additional evidence Ivanov et al., Am. J Path., 158(3): 905-919 (2001) (copy attached) referenced in the instant specification at page 16, lines 1-2, at page 24, line 3 and incorporated by reference at page 44, line 3. Ivanov et al. teaches the genus of diseases subject to the claimed methods. Applicants also respectfully point out that the number of diseases within the genus of diseases recited in the claims is fairly limited, as shown by the exemplary diseases recited within the instant Specification and in Claim 3. However, the methods would apply to any other tissue that may be found to fall within the rather narrow set of tissues that normally express MN/CA IX, but lose MN/CA IX expression upon carcinogenesis, that is, if any such tissues are later identified (possibly a doubtful event). Moreover, the case law reapplied by the Examiner in the instant Office Action is inapplicable to the circumstances of the instantly claimed methods.

Applicants respectfully conclude that for the reasons cited above and elaborated below, the "strong presumption" of adequate written description that the original pending claims have remains.

Genus of Preneoplastic/Neoplastic Diseases

Applicants respectfully refer to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement [Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001] ("Guidelines"). The Guidelines support that there is adequate written description in the specification for the claimed genera of preneoplastic/neoplastic diseases:

> **Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces**.

[Guidelines, page 1106, 3rd column; emphasis added.]

In arguing undue breadth of the claims, the Examiner contends that the Specification only discloses gastric cancer tissue samples [Office Action, at page 7], and that "the state of the art is such that it is unclear which cancers, other than gastric cancers, result in a decrease in MN/CA IX expression upon carcinogenesis." [Office Action, page 6, top ¶.] Applicants respectfully disagree, submitting that the genus of preneoplastic/neoplastic diseases that are the subject of the instantly claimed methods are adequately described in conventional art referenced in the Specification, as well as in the Specification itself.

Exemplary Prenoplastic/Neoplastic Diseases

In response to Applicants' previous response dated August 16, 2007, referring to the teaching of Pastorekova and Zavada 2004 [Cancer Therapy, 2: 245-262 (2004)], the Office Action concludes [in the passage bridging the bottom of page 7 to the top of page 8] that "based on the disclosure and the art one of skill would not recognize which cancers other than those of the stomach and gallbladder are encompassed by the genera." As explained in detail below and in the 08/16/07 Response, that conclusion is erroneous.

The number and types of species comprised within the subject genus of preneoplastic/neoplastic diseases are relatively limited. Exemplary species within the genus of diseases are described in the instant Specification at the least at page 5, lines 11-18; at page 9, lines 3-21; at page 22, line 30 to page 23, line 7; at page 23, line 30 to

page 24, line 31; and at page 45, line 31 to page 46, line 3 (original Claim 3). For example, exemplary species can be found at page 5, lines 11-15 of the Specification, which reads:

> Said tissue is preferably selected from the group consisting of gastric mucosa, gallbladder, biliary ducts, ductal cells of duodenal glands, testis including ductular efferens and rete testis, ovary including surface coelomic epithelium and rete ovarii, basal cells of hair follicles, and central nervous system choroid plexus.

In addition, original Claim 3 [at page 45, line 31 to page 46, line 3] recites the same exemplary tissues.

Ivanov et al., 2001 (copy attached)

Ivanov et al., [Am. J Path., 158(3): 905-919 (2001); copy attached], referenced in the instant specification at page 16, lines 1-2, at page 24, line 3, and incorporated by reference at page 44, line 3, performed a detailed analysis of the expression of CA IX (and of CA XII) in a large sample of cancer cell lines, fresh and archival tumor specimens, normal human tissues, and cultured cells under hypoxic conditions, and described the number of tissues which normally express MN/CA IX protein as limited: "Expression of CA IX and CA XII in normal adult tissues was detected only in highly specialized cells. . . ." [Abstract.] At page 909, under the section entitled "CA IX/CA XII Expression in Normal Adult Human Tissues Analyzed by Immunohistochemistry," Ivanov et al. states:

> High levels of CA IX expression were consistently observed in the basal cells in and near the infundibulum and medulla of the hair follicle, mesothelial cells, and coelomic epithelium of the body cavities. In the visceral organs, **high levels of CA IX expression in the epithelium were identified but limited to rete ovarii, rete testis, ductular efferens, bile ducts, pancreatic ducts, and gallbladder**. In the gastrointestinal tract, **diffuse CA IX immunoreactivity was observed in the gastric mucosa, ductal cells of Brunner's glands, and crypt cells of the duodenum, jejunum, and, to a lesser degree, in the terminal ileum and appendix. In the peripheral and central nervous systems, CA IX expression was limited to the ventricular lining cells and the choroids plexus**. Interestingly,

> mesodermal cells of the amniotic/chorionic plate of the placenta and cartilaginous tissues from joint spaces also showed variable degrees of CA IX protein expression.
>
> . . . **A summary of the distribution of expression in normal tissues is given in Table 3**, and selected normal tissues with high expression of CA IX and/or CA XII are illustrated in Figure 3.

[Emphasis added.]

That summary of normal tissues with high (diffuse) expression of CA IX in Table 4 of Ivanov et al. at page 911 basically corresponds with the subject tissues recited in pending Claim 3. As the prior art taught that cancers of several of those tissues (gastric mucosa[2], gallbladder and biliary epithelium[3]) exhibited loss of CA IX expression, one of skill in the art would reasonably expect that other normal tissues with similar high expression of CA IX, primarily normal tissues with high rates of proliferation, would also be expected to lose CA IX expression upon carcinogenesis.

Such exemplary prior art support shows that, contrary to the Examiner's statements at page 5 of the Office Action, that the Specification discloses and the prior art teaches the genus of tissue samples taken from a subject vertebrate with a disease that affects a tissue which normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis.

"Pioneering Inventions"

In response to Applicants' arguments that the claims are drawn to a pioneering invention and therefore entitled to broad claim coverage, the Examiner

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2. Pastorekova et al., "Carbonic Anhydrase IX: Analysis of stomach complementary DNA sequence and expression in human and rat alimentary tracts," Gastroenterology, 112: 398-408 (1997); Leppilampi et al., "Carbonic anhydrase isozymes IX and XII in gastric tumors," World J Gastroenterol, 9: 1398-1403 (2003); and Pastorekova and Zavada, "Carbonic anhydrase IX (CA IX) as a potential target for cancer therapy," Cancer Therapy, 2: 245-262 (2004) [cited in the Specification at page 4, line 1].

3. Saarnio et al., "Transmembrane carbonic anhydrase, MN/CA IX, is a potential biomarker for biliary tumours," J. Hepatology, 35: 643-649 (2001) [cited in the Specification at page 24, line 16]. A copy of Saarnio et al. is attached.

erroneously contends that "[w]ithout demonstrating a trend between a particular prognosis and expression levels of MN/CA IX protein in samples from numerous types of diseases . . . , one would not predict that all samples comprising preneoplastic/ neoplastic tissue . . . would function as claimed." [Office Action, at page 8.] Applicants respectfully counter that the standard for enablement is not absolute certainty, but whether "it is more likely than not true." [MPEP § 2164.07.] Case law supports the view that some inoperative embodiments are permissible, and that the subject matter within a claim need not be shown to have the same degree of utility.

As in their previous response dated August 16, 2007, Applicants respectfully refer to the Guidelines for the Examination of Patent Applications under the 35 U.S.C. 112, ¶1 "Written Description" Requirement [Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001] ("Guidelines"). The Guidelines clearly state that "[d]escription of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." [Guidelines, page 1106, 3rd column; emphasis added.]

The concept underlying the policy in regard to "pioneering inventions" is to incentivize not only

> invention and its disclosure, but to **its prompt early disclosure.** . . .
>
> . . . To restrict appellants to the crystalline form disclosed . . . would be a poor way to stimulate invention, and particularly to **encourage its early disclosure**.

[In re Hogan and Banks, 194 USPQ 527, 537 (CCPA 1977); emphasis added.]

The Applicants were the first to recognize the claimed prognostic methods in relation to, as pointed out herein, a relatively small set of tissues. If the Applicants had waited until they tested each of the tissues, before disclosing the methods to the public, the public, especially clinicians, would be poorer for such delayed knowledge. There is a quid pro quo for early disclosure, and the "quo" involves not requiring that each species of a genus be tested, particularly when one of skill in the art would reasonably expect that the mechanics underlying the phenomenon that MN/CA IX expressed in a normal tissue that loses expression upon carcinogenesis, based on the

instant disclosure is shown, in the representative examples, to present a poorer prognosis when then expressed at a higher level. That renewed expression is not a good sign for the patient's prognosis as taught by the instant application, that is, the patient has a poorer prognosis, than a patient whose tumor tissue (from the small set of tissues to which the invention applies) is not exhibiting such renewed MN/CA IX expression. The information of that renewed MN/CA IX expression is of significant value to the clinician in treating the patient with that poorer prognosis.

Inoperative Embodiments

As the CCPA has emphasized, the subject matter within a claim need not be shown to have the same degree of utility. [In re Gardner, 177 USPQ 396 (CCPA 1973), reh'g denied, 178 USPQ 149 (CCPA 1973); In re Fouche, 169 USPQ 429 (CCPA 1971).] Further, as the Board of Patent Appeals and Interferences stated in Horton v. Stevens, 7 USPQ2d 1245 at 1247 (Bd. Pat. App. & Int'f. 1988): "The mere fact that a claim embraces undisclosed or inoperative species or embodiments does not necessarily render it unduly broad. In re Dinh-Nguyen, . . . , 181 USPQ 46 (CCPA 1974); In re Bowen, ... 181 USPQ 46 (CCPA 1974). . . ." [See also, Atlas Powder Co. v. E. E. du Pont de Nemours & Co., 224 USPQ 409 (Fed. Cir. 1984).]

Robertson et al., 2004 (copy attached)

Applicants further respectfully submit as evidence relatively recent data [Robertson et al., Cancer Res., 64: 6160-6165 (September 1, 2004); copy attached; cited in Applicants' previous response, at page 33] showing that MN/CA IX not only is expressed by many tumors, but also has an important functional role favoring tumor growth, contributing to the aggressiveness of virtually any tumor, further substantiating the prediction that higher-than-expected CA IX expression in a tumor, whatever the normal CA IX expression of the healthy tissue, predicts a poorer-than-expected prognosis.

Robertson et al. (2004) (copy attached) pointed out that "several clinical studies show a clear relationship between high CAIX levels in tumors and a poor prognosis. . . . However, whether CAIX expression is simply a marker of hypoxia or a

mechanism of adaptation has not been determined, and the cellular function of CAIX remains unclear." [Robertson et al., at page 6160, col. 1.] They therefore used RNA interference (RNAi) to examine the function of CA IX in MDA 468 and MDA231 breast carcinoma cells, which RNAi resulted in growth delay in dense monolayer culture and a 50% reduction in clonogenic survival under hypoxia. The authors concluded at page 6164 (col. 2) that "CA IX is important for the growth and survival of tumor cells under normoxia and hypoxia." In other words, MN/CA IX has an important functional role in tumorigenesis, most likely mediated by its influence on microenvironmental pH. [*Id.*]

Applicants respectfully conclude that not only are the claims drawn to a pioneering invention, but that more recent data support the prediction that high CA IX expression in a tumor would be associated with a poorer prognosis in a broad range of precancerous and cancerous diseases.

Inapplicability of Case Law Cited

At page 9 of the Office Action, the Examiner reapplies "cases such as Lilly" [i.e., University of California v. Eli Lilly and Co., 43 USPQ2d 1398 at 1406 (Fed. Cir. 1997)], stating that "while the inventions at issue in cases such as Lilly were products *per se*, the holdings of those cases are also applicable to claims such as those at issue here since a disclosure that does not adequately describe a product itself cannot adequately describe a method of using that product." Applicants again respectfully submit that the Lilly case cited by the Examiner at page 10 of the Office Action is not relevant to the instant claims. The "genetic material" found to lack written description in Eli Lilly was the human insulin gene for which the native DNA sequence was not provided. In the instant case, the claimed methods use the product **MN/CA IX protein or MN/CA IX polypeptide**, which product is clearly adequately described by the instant specification. The product being used according to the claims is not the disease; moreover, the specific diseases comprised within the genus are basically finite and not unknown, unlike the sequence of human insulin gene in Eli Lilly. Methods to detect and quantitate levels of MN/CA IX are well known in the art. The genus of samples to be tested and how to handle such samples are well known in the art.

No undue experimentation is required to identify as in the Eli Lilly case an unknown, unisolated gene. Applicants respectfully conclude that for the reasons detailed above, the Eli Lilly case reapplied in the instant Office Action is inapposite and inapplicable to the circumstances of the instantly claimed methods.

Written Description Conclusion

Applicants respectfully conclude that the Applicants have shown by the above remarks, evidence and argument that the "strong presumption that an adequate description of the claimed invention is present when the application is filed . . ." [MPEP § 2163] is warranted in regard to the pending claims. Applicants respectfully remind the Examiner that the "rejection of an original claim for lack of written description should be rare . . ." [PTO's Written Description Guidelines] and request that the subject rejection be reconsidered and withdrawn.

III. 35 USC 112, First Paragraph (Enablement)

The rejection of Claims 1-11, 14, 16 and 18-24 under 35 USC 112, first paragraph "for failing to comply with the enablement requirement, is maintained. . . ." [Office Action page 9.]. The Examiner argues that the Specification lacks enablement because the Specification,

> [w]hile being enabling for a method of predicting survival of a patient with gastric cancer ... does not reasonably provide enablement for a method which is prognostic for every preneoplastic/neoplastic disease afflicting a subject vertebrate, wherein said disease affects a tissue, which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis, comprising . . . (d) determining that said subject vertebrate has every type of poorer prognosis. . . .

[Office Action, at pages 9-10; emphasis in the original.] Applicants first question what the Examiner means by "every type of prognosis"? The clinical significance of a prognosis is most often simply is it poorer or better; if poorer, it signifies the necessity of using more aggressive therapy, and particularly in the case wherein MN/CA IX is the

marker, treatment for hypoxic tumors, in that MN/*CA9* is one of the most, if not the most, tightly regulated by hypoxia genes to be identified so far.

Again, Applicants respectfully rely upon the arguments responding to the enablement rejection in their 08/16/07 Response, and incorporate that response herein by reference. Applicants respectfully traverse, submitting that for enablement, the burden of proof is upon the Examiner to challenge a presumptively enabling disclosure [MPEP § 2164.04], and no evidence has been presented as to why the methods would not work as claimed.

Applicants respectfully submit that once a pattern of prognosis for a genus of diseases is established, it is conventional knowledge to apply those patterns for those diseases, in the absence of evidence to the contrary. The standard for enablement is not absolute certainty, but whether "it is more likely than not true" [MPEP § 2164.07]; and case law supports the view that some inoperative embodiments are permissible.

An "applicant does not have to provide evidence sufficient to establish that an asserted utility is true 'beyond a reasonable doubt.' In re Irons, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility **is more likely than not true**." [MPEP § 2164.07.]

In re Marzocchi

The Federal Circuit quoted from In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971) in In re Brana, 34 USPQ2d 1437 at 1441 (Fed. Cir. 1995) as follows:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

[Emphasis in the original.]

MPEP § 2164.04 entitled "Burden on the Examiner Under the Enablement Requirement" directs that the initial burden of proof to challenge a presumptively

enabling disclosure is upon the Examiner. The patent case law, as well as the MPEP, makes clear that in accordance with case law, statements in a patent specification relied upon for enabling support that correspond in scope to a claimed invention "*must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of" those statements. [In re Marzocchi, supra; italicized emphasis in the original; underlined emphasis added.] Applicants respectfully submit that "there is no reason to doubt the objective truth" of statements in the Specification upon which Applicants rely for enabling support.

Applicants respectfully point out that at the time of filing an application, an applicant need not have any examples. An invention may be constructively reduced to practice by filing an application with no working examples at all or with paper examples. As the Federal Circuit has stated:

> The first paragraph of § 112 requires nothing more than objective enablement. *In re Marzocchi*, . . . , 169 USPQ 367, 369 (CCPA 1971). How such a teaching is set forth either by the use of illustrative examples or by broad terminology, is irrelevant.

[In re Vaeck, 20 USPQ2d 1438 at 1445 (Fed. Cir. 1991); emphasis added.]

The 08/16/07 Response pointed out in detail at pages 32-37 how the Specification teaches how the claimed methods can be used for the range of diseases, tissue samples, types of prognosis, and variants of MN/CA IX proteins/polypeptides, corresponding in scope with the breadth of the claims.

Applicants further respectfully argue as in the above response to the 35 USC 112, paragraph 1, written description rejection, that inoperative embodiments are permissible, and that in addition, the recent data reported in Robertson et al. 2004 (indicating MN/CA IX's functional role in tumorigenesis) support that the novel methods of the invention would work as claimed. Further, Applicants respectfully maintain that the Examiner has not provided any examples where the claimed prognostic methods do not work for any type of prognosis of preneoplastic/neoplastic diseases of tissues, where MN/CA IX is normally expressed but expression is lost or diminished upon carcinogenesis.

Types of Prognosis

As in the previous Office Action, the Examiner argues that the Specification is only enabled for prognostic methods for a patient with gastric cancer, comprising determining that "said patient has a prognosis of **shorter survival** than the average subject with gastric cancer . . ." [emphasis added], not "every type of poorer prognosis. . . ." [See Office Action, bottom of page 9, middle of page 10, middle of page 11, top of page 12, and middle of page 15.] To support that contention, the Office Action again cites Tockman et al., 1992, stating:

> Tockman 1992 teaches a method that is used to identify diagnostic and prognostic markers. Tockman et al. teaches that prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials. . . .

[Office Action, middle of page 14.]

Tockman et al. 1992

With respect to the Examiner's arguments regarding Tockman et al. 1992, Applicants first direct the Examiner's attention to the 08/16/07 Response at page 33-34, wherein Tockman et al. issues are addressed. Then, Applicants respectfully point out that in the instant case, in view of the disclosure of the instant Specification, all that is left to one of skill in the art to perform the claimed methods for a particular subject preneoplastic/neoplastic disease would be routine experimentation.

As pointed out above, the number of preneoplastic/neoplastic diseases to which the claimed methods apply is relatively small. As for correlating a tumor marker with a particular prognosis, one of skill in the art typically engages in such routine experimentation, and would be enabled to do so. As stated by the Examiner at page 14 of the Office Action, Tockman 1992 refers to acknowledged [i.e., conventional art] disease end points, and "[a] particular prognosis is a disease end point that is obviously amenable to the methods taught by Tockman et al." There is no suggestion in Tockman et al. 1992 that one of skill in the art would not know how to correlate a tumor marker with a particular prognosis.

Nor does Tockman et al. 1992 describe any subject preneoplastic/neoplastic disease of a tissue in which normal MN/CA IX expression is lost upon carcinogenesis, and in which renewed MN/CA IX expression is associated with a better prognosis.

To summarize, Tockman et al. 1992 does not constitute "evidence to the contrary".

Predictability of Prognosis Using MN/CA IX

Applicants respectfully point out that the link between high MN/CA IX expression and poor prognosis has established in general for tissues in which MN/CA IX is normally not expressed [Pastorekova and Zavada 2004, at page 251, col. 1]. MN/CA IX behaves predictably in those tissues, with the one apparent exception being renal cell carcinoma (RCC), but that "exception" is consistent with what is known about MN/CA IX and prognosis [discussed infra]. The instant invention addresses the other type of tissues, those in which MN/CA IX **is** normally expressed. As a pattern for MN/CA IX and prognosis has been determined in the first set of tissues, once the relationship between MN/CA IX expression and prognosis is established in the second set of tissues, there is no reason to expect any variation from the pattern. The Specification at page 42, lines 24-27 notes that the inventors had concluded that

> **preneoplastic/neoplastic diseases having similar CA IX expression patterns as that of gastric cancer would also be subject to the prognostic methods disclosed herein.**

[Emphasis added.]

The instant Specification teaches [at page 42, lines 11-27] that renewed expression of MN/CA IX in tumor cells could signify hypoxia or tumor progression and corresponding poorer prognosis in diseases similar to gastric cancer. As pointed out in Applicant's previous response dated August 16, 2007 at page 34, and above in the written description section, MN/CA IX is unique in its association with tumor growth: "CA IX is not only a tumor marker but appears directly involved in the oncogenesis of different types of tumors" [Driessen et al., Ann Surg., 243(3): 334–340 at page 339 (2006); copy attached.] In the absence of any evidence to the contrary, MN/CA IX's

expression patterns in preneoplastic/neoplastic diseases are likely to apply to tissues with analogous normal MN/CA IX expression patterns.

Renal Cell Carcinoma

At pages 14-15 of the Office Action, the Examiner alleges that "the unpredictability of said theory is highlighted in Pastorekov [sic] and Zavada which teaches that a subject with one cancer having a high MN/CA IX expression level would have the *opposite* prognosis as a patient with a different cancer that has a high MN/CA IX expression. . . ." The Examiner is referring to renal cell carcinoma [RCC], in which a lower MN/CA IX expression correlates with a poor survival [Pastorekova and Zavada, Cancer Therapy, 2: 245-262 (2004); at page 251, col. 1]. Applicants respectfully submit that the relationship of MN/CA IX to prognosis in that one exceptional cancer, RCC, is consistent with what is known about MN/CA IX and cancer prognosis as taught by the instant specification and Robertson et al. 2004.

In citing RCC as the exception to MN/CA IX prognostic relationships, Pastorekova and Zavada [Cancer Therapy, 2: 245-262 (2004)] refer to the possible reason for the RCC anomaly at page 251 (top of col. 2): "It is not clear, whether the expression of CA IX in RCC is predominantly a function of *VHL* gene mutation or whether it reflects also other factors. . . ." RCC is an unusual cancer, in that MN/CA IX overexpression in most RCC cells results from deregulation of HIF-1α (and subsequently of MN/CA IX) by a faulty VHL [von Hippel-Lindau] repressor, not by hypoxic stimulation of MN/CA IX expression [Ashida et al., J Cancer Res Clin Oncol., 128(10): 561-568 (2002); copy attached]. That difference in the source of MN/CA IX overexpression is important, because MN/CA IX apparently requires hypoxia for its enzymatic activation as well [Svastova et al., FEBS Lett., 577(3): 439-445 (2004); copy attached].

In other words, RCC is one cancer identified wherein MN/CA IX may be overexpressed but not always completely activated. Based on the findings of Robertson et al., 2004, one would expect that inactive MN/CA IX would not influence microenvironmental pH and therefore would not promote tumor growth and survival; and as "[m]ost of the complete CA IX is integrated in the cell membrane as a trimer . . ."

[Pastorekova and Zavada 2004, at page 253, bottom of col.1], overexpression of inactive MN/CA IX might interfere with any MN/CA IX activated by local hypoxia in advanced tumors, resulting in an improved prognosis. Applicants respectfully argue that the contrary findings for MN/CA IX and prognosis in RCC are consistent with a link between increased hypoxic expression of MN/CA IX and poor prognosis.

The Examiner states that

> in regards to the theory that renewed expression of MN/CA IX in tumor cells could signify hypoxia or tumor progression and corresponding poorer prognosis in diseases similar to gastric cancer . . . , the claimed methods are drawn to *prognostic* methods based on MN/CA IX expression. How MN/CA IX may affect tumor progression or a particular prognosis is not claimed.

[Office Action, bottom of page 14; emphasis in the original.] Applicants respectfully submit that they did not understand the above point. Applicants are unsure, for example, whether the Examiner is indicating that, for enablement of the claims, it is necessary to identify the mechanism by which higher MN/CA IX leads to a poorer prognosis. If so, Applicants respectfully disagree, and respectfully reiterate that if MN/CA IX has been shown (since the priority date of the instant application) functionally to promote tumor progression [Robertson et al., 2004], one of skill in the art would predict that higher MN/CA IX levels would correlate with poorer prognosis.

Undue Experimentation

At page 15 of the Office Action, the Examiner contends that

> [d]etermining (1) which preneoplastic/ neoplastic diseases affect a tissue which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis and (2) determining whether expression levels of MN/CA IX correlate with survival, disease recurrence, and response to treatment in subjects with [the subject] preneoplastic/neoplastic diseases . . . , . . . would require undue experimentation.

Applicants have addressed above the enablement issue regarding "which preneoplastic/neoplastic diseases affect a tissue which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon

carcinogenesis." [Point 1] Also, Robertson et al. 2004 and others clearly predict that MN/CA IX levels should "correlate with survival, disease recurrence, and response to treatment in subjects . . . ," as MN/CA IX has an important functional role in tumorigenesis, and one of skill in the art would therefore reasonably expect that high MN/CA IX would correlate with several endpoints of prognosis [Point 2].

Ex parte Forman

At the bottom of page 11, the Office Action refers to the factors to be considered in determining whether undue experimentation is required, as summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and states at page 11-12 that "[t]hese factors were addressed in the Office Action of 5/17/07, which demonstrates that undue experimentation would be required to determine with any predictability that the method would function as claimed."

However, Applicants respectfully point out that the Patent and Trademark Office Board of Patent Appeals and Interferences [the "Board"] also stated in Ex parte Forman that the "test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. . . ." [Ex parte Forman, 230 USPQ 546 at 547 (PTO Bd. App. & Interf. 1986).] Further, the Board in Ex parte Mark, 12 USPQ 1904 (PTO Bd. App. & Interf. 1989) reversed an examiner's undue experimentation rejection based on the "limited successful embodiments shown and the established unpredictability associated with . . . site-specific mutagenesis . . . to obtain even one biologically active mutein." The Board in reversing pointed out that

> only routine experimentation would be needed for one skilled in the art to practice the claimed invention for any given protein. The fact that a given protein may not be amenable for use in the present invention in that the cysteine residues are needed for the biological activity of the protein does not militate against a conclusion of enablement. One skilled in the art is clearly enabled to perform such work as needed to determine whether the cysteine residues of a given protein are needed for retention of biological activity.

[Id. At 1907; emphasis added.] In the instant case, one skilled in the art is clearly enabled to perform such work as needed to confirm the correlation of higher MN/CA IX

levels and poorer prognosis for a specific preneoplastic/neoplastic disease characterized initially by loss of MN/CA IX expression.

As the Federal Circuit stated in In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165 at 1174 (U.S. ITC 1983), aff'd sub nom., Massachusetts Institute of Technology v. AB Fortia, et al., 227 USPQ 428 (Fed. Cir. 1985): "Thus, the fact that experimentation may be complex . . . does not necessarily make it undue, if the art typically engages in such experimentation."

An "applicant does not have to provide evidence sufficient to establish that an asserted utility is true 'beyond a reasonable doubt.' In re Irons, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility **is more likely than not true**." [MPEP § 2164.07; emphasis added.]

Enablement Conclusion

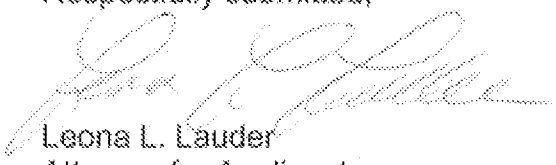
Applicants respectfully conclude that the patent case law, as well as the MPEP, makes it clear that in accordance with case law, statements in a patent specification relied upon for enabling support that correspond in scope to a claimed invention "*must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." [In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971); italicized emphasis in the original; underlined emphasis added.]

Applicants respectfully conclude that the Office has provided insufficient evidence of "reason to doubt" the objective truth of statements relied upon for enabling support in the Specification for the claimed invention. Applicants further respectfully conclude that the pending claims have the sufficient support required by the enablement requirement, and respectfully request that the Examiner withdraw the instant 35 USC § 112, first paragraph rejection.

CONCLUSION

Applicants respectfully conclude that the claims as amended are in condition for allowance, and earnestly request that the amendment to Claim 1 be entered, and that the claims be promptly allowed. If for any reason the Examiner feels that a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to telephone the undersigned Attorney for Applicants at (415) 981-2034.

Respectfully submitted,



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